West Nile virus in the United States

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In the late summer of 1999, the first known cases of West Nile virus infection in the Western Hemisphere were recorded in New York City. These first cases were the hallmarks of an outbreak of West Nile virus infection that resulted in 7 deaths among 62 confirmed cases and an estimated 8200 asymptomatic to mild infections among residents and visitors in Queens, New York. This article reviews West Nile virus and its spread in the United States since its introduction in 1999.

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Background and history of West Nile virus

West Nile virus was first isolated in 1937 from the blood of a febrile woman in the West Nile province of Uganda [1]. The virus was discovered during the course of ongoing investigations of yellow fever [2]. During subsequent investigations in Egypt, the virus was isolated from humans, birds, and mosquitoes. From these early investigations it was concluded that West Nile virus infection was basically a disease of young children, the great majority of adults being immune, and that West Nile virus is maintained in a *Culex* mosquito-bird cycle, the main mosquito vector being *C. univittatus*, a bird-feeding mosquito [2,3]. Since this initial work appeared, serologic studies have identified a widespread distribution of West Nile virus in Africa, West Asia, the Middle East, and occasionally in Europe, where outbreaks are thought to have been introduced by migrating birds (Fig. 1) [4,5•].

Virology

West Nile virus is a member of the family Flaviviridae in the genus *Flavivirus*. Antigenically, it is a member of the Japanese encephalitis virus serocomplex that includes St. Louis encephalitis, Japanese encephalitis, and Murray Valley and Kunjin (a subtype of West Nile) encephalitis viruses, among others [6]. All members of this serocomplex can be transmitted by mosquitoes, and many can cause febrile, potentially fatal, illness in humans. The close antigenic relation of viruses in the Japanese encephalitis serocomplex leads to substantial serologic cross-reaction on diagnostic tests, often resulting in the need to perform specialized tests (virus neutralization assays) to identify the infecting virus [7••].

Ecology of West Nile virus

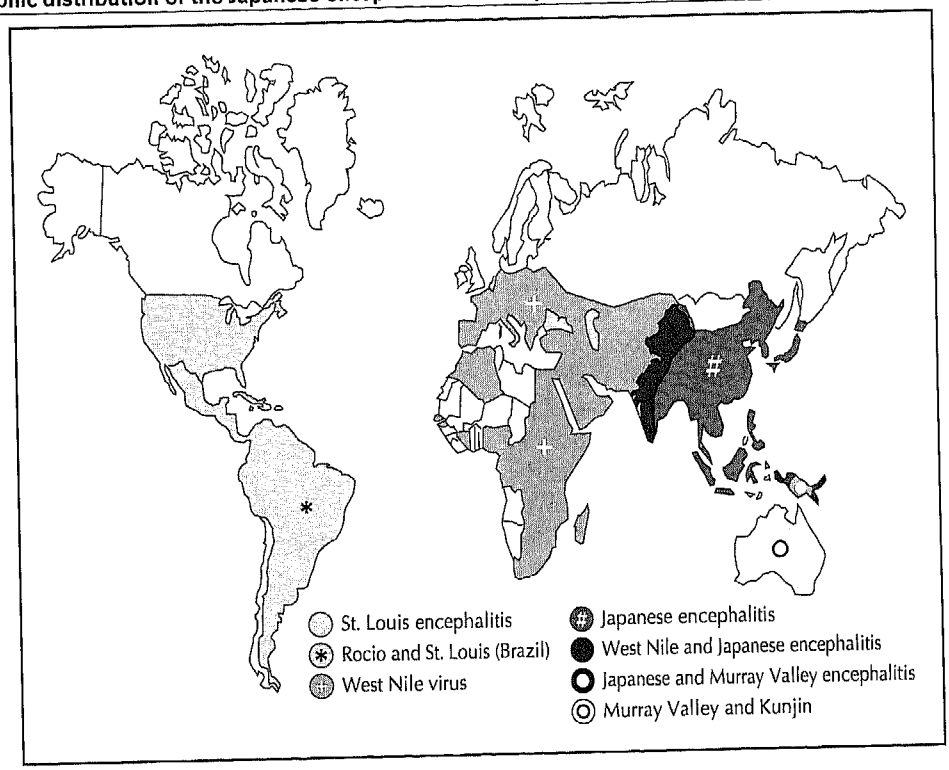
Arthropod vector

Bird-feeding mosquitoes are the principal vectors of West Nile virus; mosquitoes in the genus *Culex* serve as the predominant vector. However, the virus also has been isolated from mosquitoes in the genera *Aedes, Anopheles, Aedeomyia, Culiseta, Coquillettidia, Mansonia, Mimomyia,* and *Psorophora*. In addition, the virus has been occasionally isolated from bird-feeding argasid or amblyommine ticks [8,9••].

Vertebrate reservoir hosts

Wild birds serve as the principal hosts of West Nile virus. The virus has been isolated from both wetland and terrestrial bird species in diverse areas [5•,9•]. The virus is amplified in a natural transmission cycle between birds

Figure 1. Geographic distribution of the Japanese encephalitis serocomplex of the family Flaviviradae, 2000



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and mosquitoes. Infectious mosquitoes carry virus particles in their salivary glands and infect susceptible birds during a blood meal. After exposure, a competent bird reservoir will develop and sustain viremia for 1 to 4 days, after which lifelong immunity develops. Uninfected vector mosquitoes become infected while feeding on viremic avian hosts and, after an extrinsic incubation period, may go on to infect other susceptible hosts. The principal West Nile virus transmission cycle is that of a rural/wetland cycle involving wild, usually wetland, birds and bird-biting (orninthophilic) mosquitoes. A secondary urban transmission cycle involves synanthropic or domestic birds and mosquitoes that feed on both birds and humans (*ie*, *C. pipiens* and *C. molestus*). Although humans and other mammals may become infected through the bite of an infected mosquito, they rarely experience infectious level viremias and may be viewed as incidental or dead-end hosts [10]. However, few data are available on the role of humans or other mammals in the amplification and transmission of the virus. This area requires more research.

Clinical presentation

The classic picture of West Nile virus infection in humans is that of an influenza-like febrile illness. Clinical cases are characterized by an abrupt onset of fever (incubation period of 5–15 days), headache, backache, and myalgia lasting for 3 to 6 days. Other reported symptoms include sore throat, arthralgia, fatigue, conjunctivitis, retrobulbar pain, a maculopapular or roseola-like rash on the chest and back, lymphadenopathy, anorexia, and gastrointestinal and respiratory symptoms [9••,11••]. Neurologic infection is rare but can present as aseptic meningitis, meningoencephalitis, encephalitis, myelitis, optic neuritis, or polyradiculitis. Severe neurologic disease occurs in 1% of those infected; it occurs most commonly in the elderly and occasionally in children [4,7••, 12•,13•]. Extraneurologic infection can include hepatitis, pancreatitis, and myocarditis. Laboratory findings may include leukopenia and a slightly elevated sedimentation rate. In patients with central nervous system involvement, cerebrospinal fluid pleocytosis and elevated protein may be evident [14]. Recovery is usually complete, though it is less rapid in adults, who may experience long-term myalgia and weakness. Fatal cases have occurred, mainly among patients older than 50 years.

Diagnosis

Because West Nile virus encephalitis or meningitis is not clinically distinguishable from other viral infections of the central nervous system, specific diagnostic testing should be obtained. A case of West Nile virus infection is confirmed by any one of the following findings: (1) a fourfold rise in serum antibody titer; (2) isolation of the virus from tissue, blood, cerebrospinal fluid, or other body fluid or demonstration of viral antigen or genomic sequences in these sources; (3) capture of specific IgM antibody in cerebrospinal fluid or serum by enzyme-

linked immunosorbent assay. Because West Nile virus–specific IgM may remain detectable for several months [15], a finding of serum IgM antibody alone should be confirmed by demonstration of IgG antibodies by serologic assays such as neutralization or hemagglutination inhibition [16,17].

Epidemiology

Outbreaks

Historically, outbreaks of West Nile virus in humans have occurred infrequently in populations with high background immunity and have been associated with relatively mild disease. Notable outbreaks of West Nile fever occurred in Israel during 1951 through 1954 and in 1957. In this latter outbreak, West Nile virus became recognized as a cause of severe meningoencephalitis, principally in elderly patients [18–20]. The largest recorded epidemic caused by West Nile virus, with 3000 clinical cases recorded, occurred in 1974 in an arid region of South Africa after unusually heavy rains. Equine disease was first noted in the 1960s in Egypt and France, where it is referred to as Near Eastern equine encephalitis and lourdige, respectively [9••].

After a 20-year period of quiescence with no recorded epidemic activity, numerous outbreaks of West Nile virus infection in humans and/or horses have occurred: Algeria (1994), Morocco (1996), Romania (1996), Tunisia (1997), the Czech Republic (1997), Congo (1998), Italy (1998), Israel (1997–2000), Russia (1999), United States (1991–2001), and France (2000) [4,7••,17,21,]. With this resurgence in outbreak activity, three disturbing epidemiologic trends for West Nile virus have emerged: (1) an increase in frequency of outbreaks in humans and horses, (2) an apparent increase in more severe human disease, and (3) high rates of bird mortality in association with human outbreaks [7••]. These trends, along with genetic analysis of strains of West Nile virus isolated from recent outbreaks, suggest the evolution of new more virulent West Nile variants associated with high avian mortality and increased severity of illness in humans [12•,17,22,23].

Introduction and spread of West Nile virus in the United States

In August 1999, an unusual cluster of cases of meningoencephalitis, cause then unknown, was reported to the New York City Department of Health. The initial eight cases were among previously healthy persons between 58 and 87 years of age who had fever, changes in mental status, and profound muscle weakness [11••,24••]. Preliminary epidemiologic and environmental investigations identified arboviruses as a potential cause of the outbreak. When tested for arboviruses known to be present in the United States, specimens from all eight initial cases were positive for IgM antibody against St. Louis encephalitis virus, a flavivirus in the Japanese encephalitis serocomplex that is enzootic in the eastern United States.

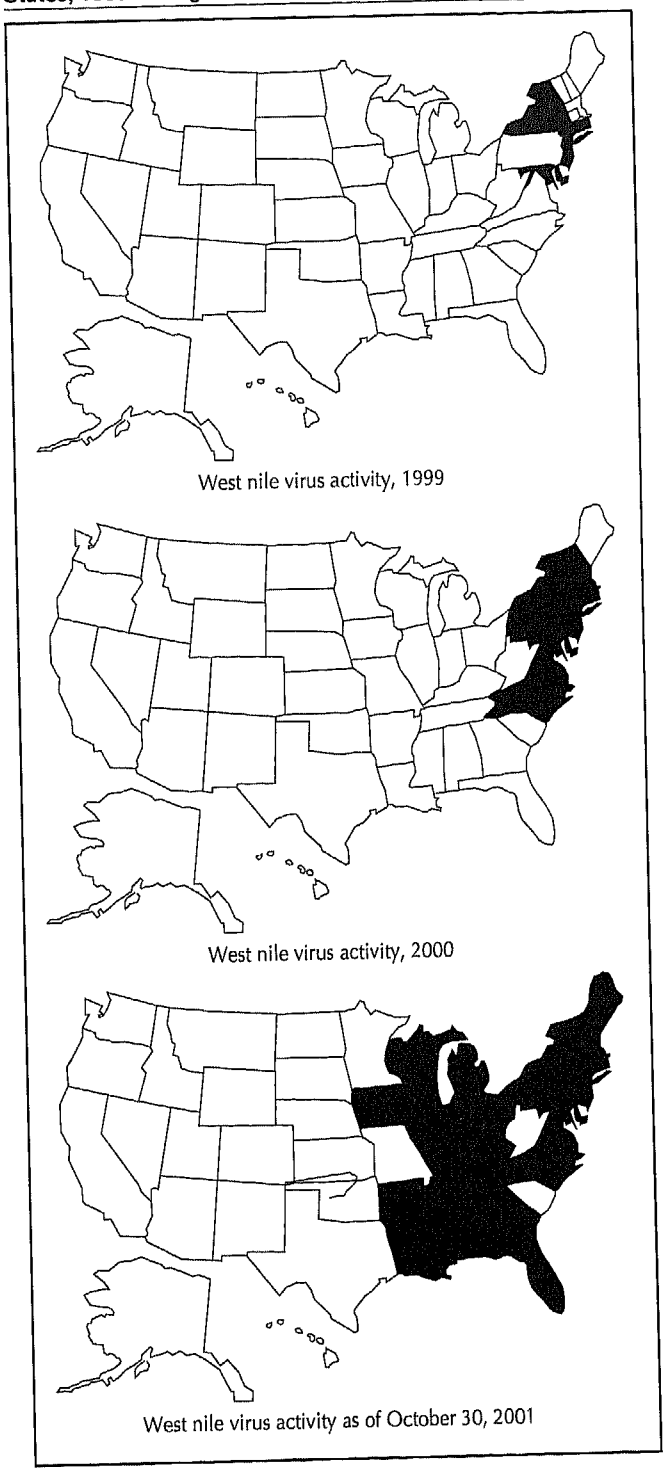
During this same period, an epizootic disease associated with the death of substantial numbers of birds was also occurring in the New York City area. Reports of dead birds (mainly crows) began to be received in late June and increased through July and August. By mid-August, dead birds were being sent to the wildlife pathologist at the New York State Department of Environmental Conservation. By late August, wild and caged birds had begun to die at the Bronx and Queens zoos, and the investigation into the cause of the epizootic intensified. Necropsy of the dead birds showed multiorgan involvement, including encephalitis. By mid-September, the federal veterinary laboratories at the U.S. Department of Agriculture and the U.S. Geological Survey had determined that the disease was caused by a virus; however, it did not appear to be St. Louis encephalitis virus or any of the other avian viruses they had tested. Because St. Louis encephalitis does not kill its avian reservoir hosts, the bird deaths and human encephalitis cases were thought to be unrelated.

Questions about the causes of both the human and the avian cases led to further testing, which by late September had identified the virus responsible for both the human and the avian outbreaks as West Nile virus. Neither West Nile virus nor human cases of infection with West Nile virus had previously been detected in the Americas.

The identification of West Nile virus as the causative agent of the outbreak allowed for an intensive surveillance effort to be established. Mosquito, avian, and human surveillance systems were rapidly established in New York City and surrounding states to document the extent of West Nile virus in the northeastern United States. During 1999, West Nile virus remained localized to New York City and areas bordering the greater New York area (Fig. 2). A total of 62 human cases of West Nile virus infection were detected in 1999. All of those cases occurred in New York City and the surrounding counties in New York State. To follow up on the true extent of symptomless and mild West Nile virus infections, a household-based seroepidemiologic survey was carried out in the fall of 1999. This survey estimated that for every case of West Nile virus encephalitis or meningitis there were 140 mild or asymptomatic infections. By extrapolation from the 59 cases of diagnosed meningoencephalitis, it was conservatively estimated that the 1999 New York outbreak consisted of 8200 West Nile virus infections [13•].

Enhanced surveillance for human encephalitis cases in the neighboring states of Connecticut and New Jersey did not detect any human West Nile virus cases in 1999. However, West Nile virus was isolated out of mosquito

Figure 2. Confirmed findings of West Nile virus in the United States, 1999 through October 30, 2001



Shaded areas represent at least one confirmed finding of West Nile virus in humans, birds, or mosquitoes.

pools in six counties in New York state (Queens, Kings, Bronx, Nassau, Suffolk, and Westchester), Hudson County in New Jersey, and Fairfield County in Connecticut. The New York and New Jersey isolates were from *Culex* species. In Connecticut, isolates of West Nile virus were obtained from pools of *C. pipiens* and *Aedes vexans* [25–27]. In addition, birds infected with West Nile virus were detected in the states of Connecticut, New York, New Jersey, and Maryland [26].

Spread of West Nile virus in 2000

After the 1999 outbreak, the Centers for Disease Control and the U.S. Department of Agriculture recommended that surveillance efforts for West Nile virus be enhanced from Massachusetts to Texas, especially along the Atlantic and Gulf coasts [28,29]. Of primary concern was whether West Nile virus transmission would persist, as had been demonstrated in the 2 years after an outbreak in Romania in 1996. The finding of viral RNA and live virus in overwintering *Culex* mosquitoes collected in New York City in January and February 2000, and the identification and recovery of West Nile virus from a hawk in February 2000, testified to the survival of the virus in the region after the mosquito season [30,31].

Twelve states along the eastern seaboard and the District of Columbia confirmed findings of West Nile virus in 2000 (Fig. 2) [32]. Human surveillance identified 21 cases of clinical West Nile virus resulting in two deaths: 14 in New York, 6 in New Jersey, and 1 in Connecticut. Mosquito surveillance identified 481 West Nile–positive mosquito pools from five states: New York, New Jersey, Pennsylvania, Connecticut, and Massachusetts. Avian surveillance identified 4323 West Nile–positive birds from 12 states (Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, and Virginia). Most positive birds were identified in New Jersey (1289), New York (1278), and Connecticut (1117). In addition, 60 equine cases of clinical West Nile virus infection were identified in seven states (Connecticut, Delaware, Massachusetts, New Jersey, New York, Pennsylvania, and Rhode Island), and six wild mammals (skunk, bat, rabbit, and chipmunk) from New York and Connecticut were identified as West Nile virus–positive.

Spread of West Nile virus in 2001

By October 30, 2001, 25 states and the District of Columbia had confirmed findings of West Nile virus (Fig. 2) [33]. Human surveillance has identified 37 confirmed clinical cases of West Nile virus, including one fatality. A 71-year-old woman from Atlanta, Georgia, was the first person to die of West Nile virus infection in 2001 in the first case ever reported from that state. Human West Nile virus infections have been reported from 7 states so far this year: Connecticut, Florida, Georgia, Maryland, New Jersey, New York, and Pennsylvania. West Nile virus–positive mosquito pools have been reported from 15 states (Connecticut, Florida, Georgia, Illinois, Kentucky, Maryland, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, and Virginia). Twenty-five states have reported a total of 5433 West Nile virus–positive birds,

including 16 states (Alabama, Arkansas, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Michigan, Mississippi, North Carolina, Ohio, Tennessee, and Wisconsin) that had not previously reported West Nile virus–positive birds. One hundred fifty-nine clinical cases of equine West Nile virus infection have been reported from 13 states (Alabama, Connecticut, Florida, Georgia, Kentucky, Louisiana, Massachusetts, Mississippi, New York, North Carolina, Pennsylvania, Tennessee, and Virginia. Of note, Canada reported its first finding of West Nile virus in 2001: birds with positive test results from Ontario [34].

Genetic analysis of West Nile virus isolates from the New York epidemic show that the virus circulating in the eastern United States in 1999 was essentially identical to a virus isolated from a dead goose in Israel in 1998. In addition, virus isolated from both avian and human brain tissue showed a high degree of homology, indicating that the same virus strain was responsible for both the human and the avian outbreaks. These data support the hypothesis that the continuing epidemic (and epizootic) of West Nile virus infection in the United States resulted from the introduction of a virus that was previously circulating in the Middle East/Mediterranean region since at least 1998 [12•,17,22,23,35].

It remains unclear how the virus was introduced to the United States. However, several possibilities exist: (1) an infected human might have entered New York, become viremic, and infected a mosquito; (2) infected migratory birds or infected captive birds imported for the captive bird trade might have introduced the virus into the native mosquito population; (3) an infected mosquito might have been transported to New York in an airplane.

Regardless of the method of introduction, what began as a focal intense epizootic of West Nile virus transmission in the New York City region in 1999 has successfully spread throughout the states of the eastern seaboard and Gulf coast of the United States and has recently radiated west and north to the Midwest and southern Canada. Seasonal surveillance data have shown a northward spread of the virus in late spring and early summer and a southward spread in late summer and fall: a pattern consistent with bird migration. The recent pattern of outbreaks in Europe suggests that viremic birds may have contributed to the dispersal of the virus. If this is also the case in the United States, West Nile virus has the potential to become established throughout the temperate and tropical regions of the Western Hemisphere [5•].

Conclusion

Since the 1990s, outbreaks of West Nile virus have increased in frequency and have occurred in regions of the world where they were previously rare or unknown. These epidemics have been caused by new variants of West Nile virus associated with increased severity of illness and high rates of avian mortality. Geographic and demographic factors will likely affect the ability of West Nile virus to establish natural foci of infection; however, continued epidemic and epizootic transmission seems likely. The initial West Nile virus epidemic in New York and the subsequent expansion of the virus throughout the eastern third of the United States emphasizes the ease with which emerging infections can become established and spread in new geographic areas. Physicians in areas with enzootic transmission of the virus should consider West Nile virus infection in their differential diagnosis of patients with summertime acute febrile illnesses. Identification of a single symptomatic human case of West Nile virus infection indicates that hundreds of other human infections may have already occurred.

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